REMARKS

Reconsideration is respectfully requested.

Claims 1-32 were previously cancelled. Claims 33-41 are pending. Claims 33 and 34 are amended. Support for the amendments is found in the specification and originally filed claims. Support for "wherein at least one member of said secondary library is not found in said primary library" is found, for example, in the specification at paragraphs 35 and 108. Support for "identifying a list of variable residue positions in said target protein" is found, for example, in the specification, Example 1, paragraphs 260-261 and Example 2, paragraph 280.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejection under 35 USC §112, second paragraph

Claims 33-41 are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states, "It is not clear what constitutes 'primary variant positions' in claim 33, step c…." While applicants believe the previously submitted claim was clear, claim 33 has been amended for technical clarity.

The term "primary variant positions" has been removed from claim 33, and applicants use the term "variable residue position". Applicants also respectfully point out that the term "variable residue position" is defined in paragraph 71 of the specification:

> [0071] The protein backbone structure contains at least one variable residue position. As is known in the art, the residues, or amino acids, of proteins are generally sequentially numbered starting with the N-terminus of the protein. Thus a protein having a methionine at it's N-terminus is said to have a methionine at residue or amino acid position 1, with the next residues as 2, 3, 4, etc. At each position, the wild type (i.e. naturally occurring) protein may have one of at least 20 amino acids, in any number of rotamers. By "variable residue position" herein is meant an amino acid position of the protein to be designed that is not fixed in the design method as a specific residue or rotamer, generally the wild-type residue or rotamer.

The Office Action also states, "…it is not clear which positions are considered 'primary variant positions', from which sequences they are obtained, and how the list of such positions is generated." Claim 33 has been amended to remove the term "primary variant position." Applicants respectfully submit that one of skill in the art will understand how to identify variable residue positions based upon the target protein, the goal of the protein design, and screening capabilities available.

Applicants note that the MPEP § 2173.02, titled "Clarity and Precision," states:

> The essential inquiry pertaining to [the requirement for definiteness of 35 U.S.C. 112, second paragraph] is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.
>
> (Emphasis added)

One of ordinary skill in the art of computational methods for designing protein variants, at the time the invention was made, had a Ph.D. in a relevant scientific field or a M.S. in a relevant scientific field with several years of work experience in computational protein design. Applicants respectfully submit that one of ordinary skill in the art of computational design of variant proteins, after reading the specification and understanding the teachings of the prior art, will understand what positions they wish to make variable for a specific target protein and specific design goals. As one example, in the specification at paragraph 259 (Example 1), the positions selected a variable residue positions were non-conserved positions within 4 Å of the four catalytic residues.

Which positions are made variant residue positions may differ from target protein to target protein, and from experiment to experiment. Applicants submit that one of ordinary skill in the art will understand the goals of the protein design specific to the target protein and experiment, and be able to identify variable residue position.

Rejections under 35 U.S.C. §§ 101/112

Claims 33-41 are rejected under 35 U.S.C. §§ 101/112 for lacking a specific asserted utility or a well established utility. Applicants respectfully submit that this ground for rejection is improper. Applicants respectfully request the rejection be withdrawn for the reasons set forth in the previous responses to the Office Actions of 2/19/2003, 9/26/2003 and 4/21/2004, and further in view of the reasons herein.

The Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility state that "[t]he claimed invention as a whole must be useful and accomplish a practical application. That is, it must produce a 'useful concrete and tangible result.' State Street, 149 F.3d at 1374-1375." Applicants respectfully submit that the claimed method results in a very useful, concrete, and tangible result - namely the ability to find novel proteins with improved characteristics – the resulting library is useful to a scientist looking to identify and generate novel proteins with desired characteristics; the resulting library is concrete in that the

contents of the library are defined (e.g., sequences) and the result is tangible since the library is a defined set of variant protein sequences that may be synthesized.

The Office Action states, "Examiner maintains that the instantly claimed method provide for generating a secondary library of as yet undetermined structure, function or biological significance which is obtained by a random combination of amino acid residues derived from a plurality of variant positions." The presently claimed method does not rely upon a purely random combination of amino acid residues in the variant residue positions. Rather, the second set of variant protein sequences is derived from application of a scoring function in step c) that generates optimized variant protein sequences filtered for desired properties. This scoring function is exemplified in Example 1. In this example, the scoring function used in step c) of amended claim 33 pares down the possible amino acids at each variable residue position. Thus, instead a library of 1,419,857 possible sequences, the method resulted in 210 possible sequences. The smaller library was enriched for optimized protein sequences, and therein is a substantial and real utility.

As stated above, one of skill in the art of computational protein design as of the time of filing of the present application will have a Ph.D. in a relevant scientific field or a Masters degree in a relevant scientific field and have worked for several years in the field. Such a person of ordinary skill will not randomly combine all possible amino acid residues for all possible variable residue positions. Thus, one of ordinary skill in the art will understand the utility of the method of the present invention and further know how to practice the method to achieve real world utility.

The Office Action states that, "there is no evidence of record or any line of reasoning that would support a conclusion that the secondary library was, as of the filing date, useful for any industrial or any pharmacological uses." Applicants submit that the use of a secondary library that is enriched for optimized protein variants does have a significant and well established utility. The secondary library has a very useful, concrete, and tangible result - namely the ability to find novel proteins with desired characteristics. The Examples provided in the specification show useful variant proteins that have industrial or pharmacological applications.

The Office Action also states, "Until some actual and specific significance can be attributed to the secondary library or even the compounds present the library, an artisan would be required to perform additional experimentation in order to determine how to use the generated secondary library. Thus, there was no immediate 'real world' utility as of the filing date." Applicants respectfully disagree with the assumption that a secondary library that is enriched for variant proteins with desired properties has no utility. The method specifically recites in step f), "synthesizing a plurality of said second set of variant sequences to generate

said secondary library of protein variants of said target protein, wherein at least one member of said secondary library is not found in said primary library." Once synthesized, these protein variants may be further screened for desired properties.

The Office Action states, "for example, for a protein having 100 residues, and assuming that all 100 positions are considered to be 'variant positions' and the residues are natural amino acids, the secondary library will be comprised of a random permutation of all 20 natural amino acid residues." Applicants respectfully submit that this characterization is not how the present method would be used by one of ordinary skill in the art. First, while all 100 residues could be considered to be "variant positions," one of ordinary skill in the art would use a scoring function to narrow down the number of possible amino acids at each variant position and narrow down the number of variant positions with two or more possible amino acid residues. This step is clearly recited in independent claim 33, step c), as currently amended.

Further more, one of skill in the art will not design a secondary library to be significantly greater that their ability to screen for variant proteins with desired properties. As the MPEP § 2173.02, titled "Clarity and Precision," states:

> The essential inquiry pertaining to [the requirement for definiteness of 35 U.S.C. 112, second paragraph] is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
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> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.
>
> (Emphasis added)

When read in light of the specification and the teachings of the prior art, one possessing the ordinary level of skill in the pertinent art (i.e. a Ph.D. in a relevant scientific field or a Masters degree in a relevant field with several years of work in computation protein design), the presently claimed method would not be used to generate a library of random permutations of all 20 natural amino acids over all 100 residues. The method contemplates that while all possible combinations may be considered computationally, the protein variants that comprise the primary library are an enriched subset of all of the possible variants. This is achieved by the use of the scoring function of step c). Only variant protein sequences that define the users design criteria will be considered part of the primary library.

The Office Action additionally cites to Shakhnovitch (1998) as evidence that prior art methods of protein design was largely unsuccessful. Applicants submit that the statement, "Most of the present experimental [protein design] approaches enjoyed only limited success," (emphasis added), actually supports patentability of the presently claimed invention. Applicants

note that the present application published July 11, 2002, about 4 years after the Shakhnovitch paper, and thus Shakhnovitch was not discussing the present method of generating secondary libraries that are enriched for proteins with desired properties. The present invention is clearly an advanced over the art described by Shakhnovitch.

Applicants respectfully draw the Examiner's attention to the requirements as further outlined in the Guidelines:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. MPEP § 2107.02 Procedural Considerations Related to Rejections for Lack of Utility, Section III.B.

Thus, the burden is shifted to the Examiner. The Applicants respectfully submit that this burden has not been met, and the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 33-40 are rejected under 35 U.S.C. 112, first paragraph. The Office Action states, "Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one of skill in the art clearly would not know how to use the claimed invention." For the reasons set forth above, Applicants respectfully submit that the claimed invention has a specific asserted utility, and one of skill in the art would understand how to use the claimed invention. Accordingly, Applicants respectfully submit that the specification fully enables the present claims, and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §§ 102 and 103

Claims 33-40 are rejected under 35 U.S.C. § 103(a) as being obvious over Topham et al. Applicants assume that the Office Action refers to Topham et al., *J. Mol. Biol.* (1993) **229**, 194-220.

Topham Does Not Teach Variant Sequences or the Generation of Variant Sequences

The Office action states, "Topham et al. teach method of modeling protein variants…." Applicants respectfully disagree with this characterization of Topham. Applicants have repeatedly searched the Topham et al. reference and have not located a single example of the computational generation of a variant protein.

Topham actually discloses a method of modeling the structure of a protein with a known sequence, but an unknown structure. Topham's goal was to identify potential structures of the protein, not changing the sequence. The evolutionary probability matrices generated by Topham are used to better align a loop of unknown structure with a loop of known structure. Topham does not teach modifying either the sequence of unknown structure or the sequence of known structure. Every calculation is to better align sequences, and thus better predict three-dimensional structure.

Applicants specifically recite in step a) of claim 33 "inputting the coordinates of said target protein into a computer". Thus, Applicants are inputting both sequence and structure as the starting point for the method. Since the structure is already known, the goal is to identify modified novel proteins that meet a users design criteria. Applicants are improving a target molecule rather than determining its possible structure.

By way of example, Applicants searched every table in Topham, as detailed herein. Table 1 lists the 174 structures used in the analysis conducted by Topham et al. The table includes the four-character PDB code (e.g. 2SNI, 1SAV, etc.), name of the protein, number of residues, resolution of the structure in Å, R_{factor} and "study". None of the listed sequences was generated by a computational design method – all of the sequences were isolated from nature.

Table 2 is a distribution of residues in high resolution protein structures of regular secondary structure amongst seven main-chain conformation states (i.e. the area of the Ramachandran plot). Applicants were unable to locate any computationally generated sequences in table 2.

Table 3 is a "Jackknife" test of template method for β-hairpins. A note at the bottom of table 3 states that predictions were based on the Dayhoff MDM250 mutation matrix (Dayhoff et al., 1983).[1] Applicants did not see any computationally generated variant sequences in table 3.

Table 4 is statistical tests of the template method for canonical residues in immunoglobulin hypervariable regions. The table lists the protein analyzed, none of them

[1] The term "mutation matrix" in the context of Dayhoff and Topham is a reference to the evolutionary mutation rate. The Applicants' use of the term "variant" is very different than Topham's use of the term "mutation." Please see **Appendix A** for more specifics regarding the Dayhoff mutation matrix and how the term mutation is used by Topham et al.

computationally generated. Again, predictions were based upon the Dayhoff MDM250 mutation matrix.

Table 5 is loop fragment scoring in modeling of residues 184-188 of proteinase K. These residues, DRYDR, are aligned with a plurality of the other naturally occurring sequences. The four character designations listed in Table 5 are protein codes for the associated PDB coordinates of proteins found in nature. For example:

> "2SNI E (181-185)" is Chain E, Subtilisin Novo, from *Bacillus amyloliquefaciens*, residues 181-185; structure deposited in the Protein Databank by C.A. McPhalen and M.N.G. James on September 5, 1988, resolution 2.1 Å;
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> "1SAV E (181-185)" is Human Annexin V, residues 181-185; structure disclosed in FEBS Lett, V.275, p 15 (1990) by R. Huber, M. Schneider, I. Mayr, J. Romisch, and E.P. Paques, resolution 2.3 Å;
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> "1ST3 A (181-185)" is Serine Protease from *Subtilisin bacillus lentus*, residues 181-185; structure deposited in the Protein Databank by D.W. Goddette, C. Paech, S.S. Yang, J.R. Mielenz, C. Bystroff, M. Wilke, and R.J. Fletterick on November 22, 1991, resolution 1.4 Å;
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> "1CSE E (181-185)" is Subtilisin Carlsberg from *Bacillus subtilis*, residues 181-185, structure deposited in the Protein Databank by W. Bode on June 3, 1988, resolution 1.2 Å;
>
> "1TEC E (185-189)" is Thermitase from T*hermoactinomyces vulgaris*, residues 185-189, structure deposited in the Protein Databank by P. Gros, B.W. Dijkstra, and W.G.J. Hol on May 24, 1989, resolution 2.2 Å;
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> "2SBT (181-185)" is Subtilisin Novo, most likely from B*acillus amyloliquefaciens* structure deposited in the Protein Databank by J. Drenth, W.G.J. Hol, J.N. Jansonius, and R. Koekoek on September 7, 1976, resolution 2.8 Å;

The homologs are all members of the protease family of enzymes. Table 5 also shows the alignment of DRYDR with several fragments from non-homologous proteins. The first three of the non-homologous protein fragments are:

> "2LIV (319-323)" is the Periplasmic Binding Protein Leucine/Isoleucine/Valine-Binding Protein from *Escherichia coli*, residues 319-323; structure deposited in the Protein Databank by J.S. Sack, M.A. Saper, and F.A. Quiocho on April 10, 1989, resolution 2.4 Å;
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> "3GRS (308-312)" is Glutathione Reductase, Oxidized Form (E), residues 308-312, structure deposited in the Protein Databank by P.A. Karplus and G.E. Schulz on February 5, 1988, resolution 1.54 Å;
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> "8CAT A (28-32)" is Catalase, residues 28-32, structure deposited in the Protein Databank by M.R.N. Murthy, T.J. Reid III, A. Sicignano, N. Tanaka, I. Fita, and M.G. Rossmann on November 15, 1984, resolution 2.5 Å;

The Office is invited to search the NIH website http://molbio.info.nih.gov/cgi-bin/pdb for all of the protein codes found in table1 and table 5 of Topham. Again, all of these sequences are fragments of naturally occurring proteins whose structures had been solved and coordinates

deposited in the PDB prior to the paper by Topham. By using different weighting functions for his alignment, Topham is able to align some non-homologous sequences as well as homologous sequences. None of the sequences shown in Table 5 are computationally generated, every one was isolated from nature.

Table 6 is a regression analysis of the template method for loop selection. Applicants did not locate any computationally generated variant protein sequences in table 6.

Applicants also searched all the figures and the text of Topham. The only protein sequences found in Topham are from naturally occurring sequences. Applicants hope the Office agrees that the sequences isolated from nature are not computationally generated variant protein sequences. Since every sequence listed in Topham is from a naturally occurring protein, Topham does not teach or suggest any computational design of a variant sequence.

Topham Teaches Generating a Library Using an Alignment Program for Modeling Only

The Office Action also states, "Topham et al teach … the steps of generating library of sequences using an alignment program." In this one aspect, Applicants agree with the characterization of Topham in the Office Action. The entire point of Topham is to improve the ability to align loops based upon evolutionary relationships between amino acids weighted for structural information, and thus improve the modeling of loops. The logic of Topham was that if a loop in an evolutionary grandparent protein is found in a later protein, this loop has a good chance to have maintained the three-dimensional structure. If a scientist can identify the same version of the loop in two "grandchild" proteins, Protein X with known structure and Protein Y with unknown structure, then the loop in Protein Y should look like the corresponding loop in Protein X. Thus, Topham was not making variant proteins; he was trying to predict the structure of loops in naturally occurring proteins with unknown structure based upon an alignment with loops in naturally occurring proteins with known structure.

Topham Does Not Teach Selecting Variant Positions or the Generation of a Secondary Library

The Office Action states, "Topham et al. teach … selecting variant positions for which frequencies of residue type occurrence (N_{freq}) and probability distribution of variant amino acid residues is determined, thus generating a secondary library." For the reasons set forth above, Applicants respectfully disagree with this characterization of Topham. Topham did not select a variant position in any of the sequences listed, since all sequences listed in Topham were generated by nature. The probability tables in Topham are only evolutionary probabilities used to better align loops in naturally occurring proteins with unknown structure based upon an alignment with loops in naturally occurring proteins with known structure. Topham did not

computationally generate any variant sequences, and thus did not select any variant positions or computationally generate a secondary library of variant sequences.

Applicants respectfully request the rejection of claims 33-40 as obvious over Topham be withdrawn, and submit that claim 33-41 are in condition for allowance.

Conclusion

Applicants respectfully assert that the present claims are in condition for immediate allowance. If an interview would expedite prosecution of the present application, the Examiner is invited to contact the undersigned at (626) 737-8089.

Respectfully submitted,
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Dated: July 27, 2006
By: _____

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